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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,686	03/30/2004	M. Youssouf Badal	134.02US	8305

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,686	BADAL ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,12,16,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 12, 16, 21-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5, 12, 16, 21-22, the complex 14-3-3/BAD in fixed tissue sample of colon cancer, are examined in the instant application.

The embodiment of claims 1-5, 12, 16, 21-22 as drawn to: 1) circulating epithelial cells as a sample as recited in claim 2, 2) the complexes other than 14-3-3/BAD, as recited in claims 3-4, and 3) breast, ovarian or prostate cancer as recited in claim 12 has been withdrawn from consideration as being drawn to non-elected invention.

Priority

The disclosure of the prior-filed application, Application No. 10/154042, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application, for reasons already set forth in paper of 05/10/07.

The response does not address this issue. It is noted that a supplemental oath or declaration is required under 37 CFR 1.67, because the claimed priority to the continuation-in-part applications SN= 10/154042 and 10/623057 is not recited in the Oath submitted on 07/20/04. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP § § 602.01 and 602.02.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 12, 16, 21-22 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons already set forth in paper of 05/10/07.

1. Claims 1-5, 12, 16, 21-22 remain rejected under 35 U.S.C. 112, second paragraph, for being indefinite.

The response asserts that the specification and the Examples in the specification teach how to correlate the differences with the disease status of the patient. The response asserts that Example 1 shows that the dimerization of PI3K to Her-3 to give the PI3K/Her-3 complex increases in breast cancer cell lines as the concentration of HRG is increased, thereby showing that the severity of cancer correlates with PI3K/Her-3 complex. The response asserts that thus, in light of the teachings of the specification, one of skill in the art would know how to determine the disease status of the patient based on the relative amounts of the complex. The response asserts that if a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claim is not explicitly described in the specification, then the requirement for an adequate written description is met.

The response has been considered but is not found to be persuasive for the following reason:

This is 112, second paragraph rejection for being indefinite, and not 112, first paragraph, enablement or written description rejection.

It is not clear a difference in the amount of tested sample as compared to a reference sample, is correlated with which status of disease, which encompasses likelihood of contracting

colon cancer, **presence or absence** of colon cancer, prognosis of colon cancer severity, or likelihood of treatment response by the patient (the instant specification, page 12, second paragraph)?

2. Claims 16, 22 remain rejected under 112, second paragraph, for being confusing.

The response asserts that that the amendment obviates the rejection.

The response has been considered but is not found to be persuasive for the following reason:

The process of how to tag and detect the complex is unclear and very confusing.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 12, 16, 21-22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The response asserts that in Example 3, the applicants simultaneously measure BAD/14-3-3 and BAD/Bcl-2 complexes in serum-starved breast cancer cell line culture (MCF-7), and the results illustrated in Figure 9. The response concludes that thus BAD/14-3-3 complex correlates with at least breast cancer.

The response has been considered but is not found to be persuasive for the following reasons:

Status of disease encompasses likelihood of contracting colon cancer, presence or absence of colon cancer, prognosis of colon cancer severity, or likelihood of treatment response by the patient (the instant specification, page 12, second paragraph).

Concerning the unpredictability of the prognosis or likehood of contracting colon cancer, or prognosis of colon cancer severity, or likelihood of treatment response by the patient, in view of the teaching of Tockman et al, of record, the response does not address this issue. Therefore, rejection remains.

Concerning detection of colon cancer, there is no correlation between detection of an increase in the amount of the complex 14-3-3/BAD in a breast cancer cell line and colon cancer tissue, because of: 1) The well known **cell culture artifact**, and 2) The unpredictability of the level of expression of a protein in **different cancers**, which have different etiology and characteristics.

Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al, 1993 (Leukemia and Lymphoma, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al, 1984 (Immunol Ser, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma,

caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu, 1973 (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Tian, J et al, 2004 (Physiol Genomics, 17: 170-182), teach culture-induced artifact in macular RPE cells, wherein 950 genes are differentially expressed between native RPE and cultured RPE cells, and wherein 2080 genes are expressed in cultured RPE cells but are not expressed in native RPE cells (abstract, p.176). Similarly, Van Dyke D L et al, 2003 (Cancer Genetics and Cytogenetics 241: 137-141), teach that random loss of chromosome 21 (monosomy 21) in patients with hematologic diseases is rare and should be confirmed by in situ hybridization (FISH), and that in most diagnosed cases the random loss of chromosome 21 is more likely due to artifact of culture of cells obtained from the patients (abstract, and p. 140, first column, last two paragraphs before acknowledgments). Zaslav A L et al, 2002 (Amer J Medical Genetics 107: 174-176), teach that prenatal mosaicism for a deletion of chromosome 10 (q23) is rare, and that most diagnosed deleted (10q) mosaicism represents culture artifact, i.e. diagnosed individuals may have a deletion at this site when their isolated cells were grown in tissue culture or subjected to low folate conditions (abstract, and p. 175, first column, paragraph under Discussion).). Kunkel, P, et al, 2001 (Neuro-oncology 3(2): 82-88), teach that teach that scatter factor/hepatocyte growth factor is overexpressed in most tumors examined, including glioblastomas, and that the lack of expression of scatter

factor/hepatocyte growth factor in most cultured glioblastoma cells is not representative of the in vivo situation, and most likely represents a culture artifact (abstract). The evidence presented thus clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays.

Further, different cancers have different etiology and characteristics, and mutation or amplification of a gene in a specific cancer is not necessarily the same as that for the same gene in another type of cancer. For example, Montesano, R et al,1996, Intl J Cancer, 69(3): 225-235, teach that two different forms of esophagus cancer, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) have different etiological and pathological characteristics, and that a comparison of p53 mutations in these two cancers shows that said mutations differ by their types, frequencies, distribution along the gene and impact on p53 protein structure (p.231, second column, first paragraph). Similarly, Burmer, GC et al, 1991, Environmental Health perspectives, 93: 27-31, teach that in contrast to sporadic colon carcinomas, mutations in c-Ki-ras are infrequently observed in carcinomas or areas of high-grade dysplasia in patients with chronic ulcerative colitis, and that differences in the frequency, and spectrum of mutations observed in sporadic colon carcinoma and pancreatic carcinoma suggest that a different class of carcinogens may be involved in the initiation of these two tumors (p.27, second column, last paragraph, bridging p.28). Busken, C et al, Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850, teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic

constitution (last five lines of the abstract). Thus based on the teaching in the art and in the specification, one cannot predict that the complex 14-4-4/BAD is overexpressed in colon cancer tissue as compared to normal colon tissue.

Further, it is not clear what constitutes a **reference sample**, which is not necessarily a control, normal colon tissue, nor what is the **corresponding** amount, which could be of any amount, because it is not clear how the amount "corresponds" to each others. In addition, a **difference** in the amount encompasses either an increase or a decrease in the amount. There is no indication that expression 14-3-3/BAD complex is decreased in colon cancer.

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 remain rejected under 35 U.S.C. 102(b) as being anticipated by Wildi et al. (2001, Gut 49:409-417), for reasons already of record in paper of 05/10/07.

The response asserts that the art does not teach that the complex is an intracellular complex.

The response has been considered but is not found to be persuasive for the following reasons:

The complex is detected by immunohistochemistry, i.e. using tissue sample, containing cells, and not a serum sample (Wildi et al, p.6, item under immunohistochemistry, and figures 6-7, on page 10). It is clear that the complex is detected in the cells, and thus is intracellular.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE

MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH-TAM DAVIS
January 12, 2008

/Larry R. Helms/
Supervisory Patent Examiner